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Phase-transfer catalyzed enantioselective α-alkylation of α-acyloxymalonates: construction of chiral α-hydroxy quaternary stereogenic centers†

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The enantioselective synthesis of α-acyloxy-α-alkylmalonates was developed as an efficient method for producing chiral α-tertiary alcohols, which are potentially valuable intermediates in the synthesis of natural products and pharmaceuticals. The efficient enantioselective α-alkylation of diphenylmethyl *tert*-butyl α-acyloxymalonates was accomplished *via* phase-transfer catalysis in the presence of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide to afford the corresponding α-acyloxy-α-alkylmalonates at high chemical (up to 99%) and optical (up to 93% ee) yields, which could be readily converted to versatile chiral intermediates with a chiral α-tertiary alcohol group.

Chiral α-hydroxymalonates and their related compounds are potentially valuable intermediates for the synthesis of natural products and pharmaceuticals (Fig. 1).[1] Furthermore, α-hydroxymalonate can be easily modified to α,β-dihydroxy esters or glycerols *via* the chemical conversion of two esters. There are many enantioselective synthetic methods for the α-hydroxy-β-ketoester system.[2,3] However, the enantioselective synthetic methods of α-hydroxymalonates have been mostly achieved by the enzymatic desymmetrization of prochiral malonates,[4] and there is only one chemical synthetic method *via* the enantioselective direct α-hydroxylation of prochiral malonate, which uses oxazine as an oxidant in the presence of Ni complex of (*R*,*R*)-DBFOX-Ph as an organometallic catalyst and was reported by Shibata group.[5]

Recently, we reported new synthetic methods to produce chiral malonates in high chemical yields and enantioselectivities *via* the phase-transfer catalytic (PTC) desymmetrizing malonates system in the presence of chiral quaternary ammonium salts. We successfully demonstrated the usefulness of these synthetic methods by applying them to synthesize various chiral building blocks with tertiary or quaternary carbon centers.[6]

We planned to develop a new synthetic method of chiral quaternary α-hydroxymalonates using the well-established enantioselective phase-transfer catalytic α-alkylation of malonates (Scheme 1B).[7] The incorporation of a hydroxyl group into the α-position of malonates and the subsequent enantioselective α-alkylation under phase-transfer catalysis conditions, which is a key step for the asymmetric induction, would yield chiral quaternary α-hydroxymalonates which is a reverse

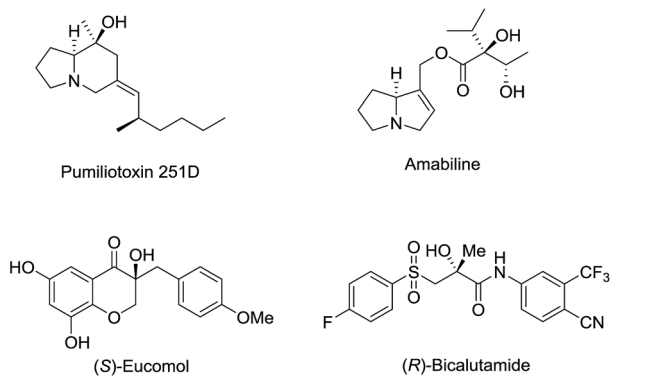
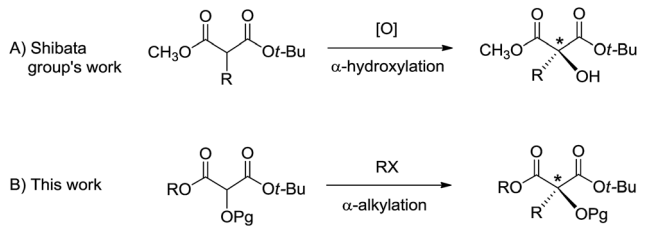


Fig. 1 Bioactive ingredients with an α-hydroxy quaternary stereogenic center.



Scheme 1 Strategy for synthesizing chiral α-hydroxymalonates.

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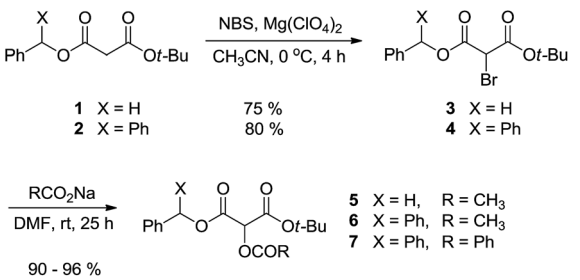
strategy to that used in the Shibata group's work (Scheme 1A).[5] The advantage of our strategy is that various chiral compounds are easily available only by changing the alkylating reagents. Herein, we report a new and highly efficient enantioselective synthetic method for α-acyloxy-α-alkylmalonates *via* asymmetric phase-transfer catalysis.

First, we designed enantiotopic unsymmetrical α-hydroxymalonates as the substrates for PTC α-alkylation. Because both the diphenylmethyl ester group and the *tert*-butyl ester group were essential for the high enantioselectivity in previous enantioselective PTC α-alkylations of the malonate system,[6a] we used diphenylmethyl *tert*-butyl malonate (**2**) as a template of the substrates with benzyl *tert*-butyl malonate (**1**) (Scheme 2). α-Acyloxymalonates **5–7** were prepared from malonates **1** and **2** in 2 steps. The α-bromination of malonates **1** and **2** using *N*-bromosuccinimide (NBS) in the presence of magnesium perchlorate under acetonitrile produced α-bromomalonates **3** and **4**, respectively.[3k] Substitutions of α-bromides with sodium acetate or sodium benzoate successfully produced the corresponding α-acyloxymalonates **5–7**.

In a preliminary study, the substrate efficiency of the prepared substrates were examined by α-allylation under typical PTC conditions based on previous reports.[6] Enantioselective PTC allylation of **5–7** was performed in the presence of the chiral quaternary ammonium salts (**8–11**) (Fig. 2),[8] allyl bromide (5.0 equiv.) and 50% KOH (aq., 5.0 equiv.) at room temperature in toluene (Table 1).



Scheme 2 Preparation of diphenylmethyl *tert*-butyl α-acyloxy malonates.

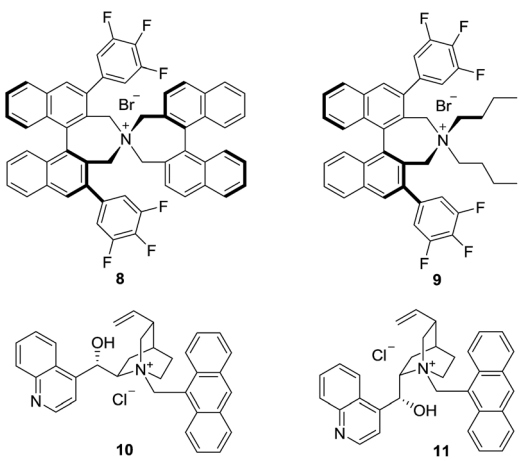
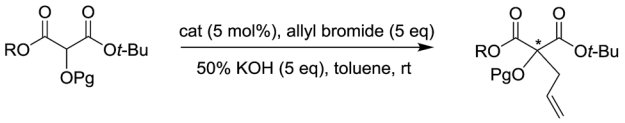
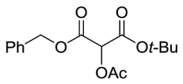
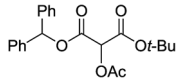
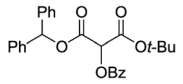


Fig. 2 Representative chiral phase-transfer catalysts.

Table 1 Enantioselective PTC allylation of α-acyloxymalonates[a]



Entry	Malonate		Cat.	Time (h)	Yield[b] (%)	ee[c] (%)
1		**5**	**8**	2	98	42
2		**6**	**8**	4	90	76
3		**7**	**8**	2	89	79
4			**9**	4	80	12
5			**10**	6	62	24
6			**11**	6	32	21

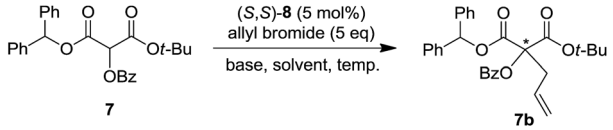
[a] Reactions were performed with 5.0 equiv. of allyl bromide and 5.0 equiv. of 50% KOH (aq.) under the given conditions. [b] Isolated yields. [c] Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H).

As shown in Table 1, all malonate substrates successfully produced α-allylated products. Malonate **6** showed a higher enantioselectivity than malonate **5** in the presence of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**8**) (entries 1 and 2). One more phenyl ring may be responsible for the higher enantioselectivity *via* the π–π stacking interaction between the substrate and PTC catalyst **8**. In the case of the α-acyloxy group, the α-benzoate group showed a slightly higher enantioselectivity than the acetate group, with comparable chemical yield in the presence of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**8**). However, *N*,*N*-dibutylbinaphthyl-derived catalyst **9** and *cinchona*-derived catalysts (**10** and **11**) have significantly lower enantioselectivities than **8**, which is consistent with the previous result (entries 3–6).[6a]

Next, we selected malonate **7** to optimize the reaction conditions. The PTC allylation of **7** was performed in the presence of the best catalyst **8** under variable base, solvent and temperature conditions. As shown in Table 2, in general, the enantioselectivity did not significantly depend on the base conditions. However, the solid CsOH exhibited notably lower chemical yields (entry 4, 9%). The variation of the reaction solvent also could not significantly increase both enantioselectivity and chemical yield (entry 2, entries 5–7). In case of temperature conditions, the lower reaction temperatures resulted in the higher enantioselectivity except −40 °C (entry 2, entries 8–9). However, the reaction time increased with a decrease in temperature, which resulted in a notably longer reaction time at −40 °C (entry 10). Finally, 50% CsOH base under toluene at −20 °C were selected as the optimized reaction conditions, considering the enantioselectivity, chemical yield, and reaction time (entry 9; 94%, 87% ee).

Under the optimized reaction condition (Table 2, entry 9), the scope and limitations of the enantioselective PTC alkylation of **7** with various electrophiles were studied (Table 3). The activated allylic and benzylic halides yielded high enantioselectivities.

Table 2 Optimization of the PTC benzylation of α-benzyloxy malonates 7 [a]



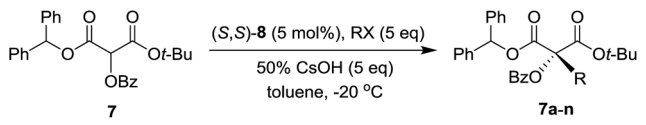
Entry	Base	T (°C)	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	50% KOH	rt	Toluene	2	89	79
2	50% CsOH	rt	Toluene	2	90	80
3	KOH (s)	rt	Toluene	15	72	80
4	CsOH (s)	rt	Toluene	15	9	80
5	50% CsOH	rt	Xylene	4	99	78
6	50% CsOH	rt	Mesitylene	4	86	79
7	50% CsOH	rt	Cyclopentylmethyl ether	4	81	79
8	50% CsOH	0	Toluene	4	90	86
9	50% CsOH	−20	Toluene	5	94	87
10	50% CsOH	−40	Toluene	16	71	75

[a] Reactions were performed with 5.0 equiv. of allyl bromide and 5.0 equiv. under the given conditions. [b] Isolated yields. [c] Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H).

However, unactivated hexyl iodide showed slightly lower enantioselectivity at 0 °C with relatively longer reaction time (Table 3, entry 1). The high enantioselectivities (up to 93% ee) in Table 3 indicate that this reaction system is a notably efficient enantioselective synthetic method for α-benzoyloxy-α-alkylmalonates.

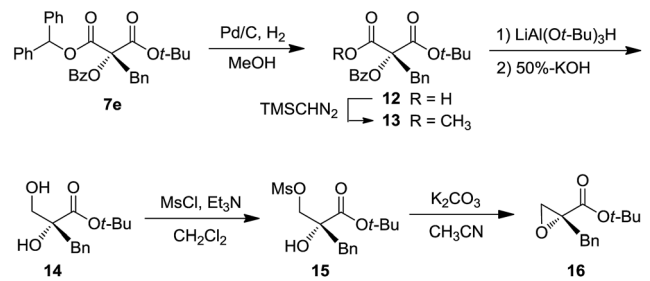
The synthetic potential of this method was demonstrated *via* the synthesis of α,β-dihydroxyester (**14**), α,β-epoxyester (**16**), and 1,2-diol (**17**), as exemplified in Schemes 3 and 4. Catalytic hydrogenation of **7e** with Pd/C–H_2 in methanol afforded the corresponding mono acid **12** that was converted to the corresponding methyl ester **13** by the treatment of trimethylsilyldiazomethane. The reduction of **13** using LiAl(O*t*-Bu)$_3$H, followed by basic hydrolysis using 50%-KOH provided diol **14**. Finally, the mono mesylation of **14**, followed by intramolecular epoxidation in the presence of K_2CO_3 under acetonitrile afforded epoxide **16** (Scheme 3). The absolute configuration of **7e** was assigned as *R* by the chemical conversion to a known compound (**17**). The reduction of **16** using $LiAlH_4$ successfully afforded diol (*S*)-**17** {$[\alpha]_D^{20} = -9.6°$ (*c* 1.0, EtOH 95%); lit.[9] (*R*)-**17**, $[\alpha]_D^{20} = +11.4°$ (*c* 1.0, EtOH 95%), 94% ee} (Scheme 4).

Table 3 Enantioselective synthesis of α-benzoyloxy-α-alkylmalonates *via* PTC alkylation[a]

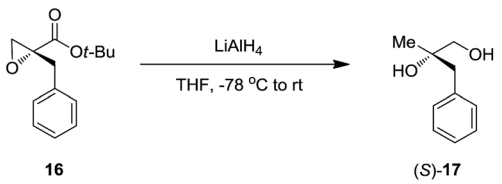


Entry	RX	Time (h)	Yield[b] (%)	ee[c] (%)
1[d]	$CH_3(CH_2)_4CH_2I$ (**a**)	19	99	75
2	CH_2=$CHCH_2Br$ (**b**)	2	94	87
3	CH_2=$C(CH_3)CH_2Br$ (**c**)	2	75	91
4	CH_2=$C(Br)CH_2Br$ (**d**)	15	89	93
5	$PhCH_2Br$ (**e**)	3	99	91(*R*)[e]
6	4-Me-$PhCH_2Br$ (**f**)	3	93	91
7	4-*t*-Bu-$PhCH_2Br$ (**g**)	4	95	91
8	3-CH_3O-$PhCH_2Br$ (**h**)	2	91	93
9	3,5-$(CH_3O)_2$-$PhCH_2Br$ (**i**)	2	93	91
10	4-F-$PhCH_2Br$ (**j**)	3	90	85
11	4-Cl-$PhCH_2Br$ (**k**)	3	92	80
12	4-Br-$PhCH_2Br$ (**l**)	3	88	93
13	4-NO_2-$PhCH_2Br$ (**m**)	2	92	81
14	β-Naphthyl-CH_2Br (**n**)	3	72	88

[a] Reactions were performed with 5.0 equiv. of alkyl bromides and 5.0 equiv. of 50% CsOH (aq.) under the given conditions. [b] Isolated yields. [c] Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H). [d] The reaction was performed under 0 °C. [e] Absolute configuration of **7e** was confirmed as ***R*** based on the (*S*)-**17** prepared from **7e** (Scheme 4).



Scheme 3 Derivatizations of chiral malonate **7e**.



Scheme 4 Conversion of **16** into (*S*)-**17** to confirm the absolute configuration of **7e**.

In conclusion, an enantioselective synthetic method for α-benzoyloxy-α-alkylmalonates *via* PTC alkylation was developed. The asymmetric PTC α-alkylation of diphenylmethyl-*tert*-butyl α-benzoyloxy-malonates produced the corresponding α-benzoyloxy-α-alkylmalonates with high chemical (up to 99%) and optical (up to 93% ee) yields. Our new catalytic system provides an attractive synthetic method for versatile chiral building blocks, which can be readily converted to chiral target molecules with α-hydroxy quaternary stereogenic centers. Further applications and extension to the α-acylthiomalonate system are currently under investigation and will be reported in due date.

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